Journal of Rare Diseases

REVIEW

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Neuro-cognitive complications of nephropathic cystinosis

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Abstract

Purpose To review the neuro-cognitive complications of nephropathic cystinosis.

Methods Review of published information on neurological and cognitive complications of cystinosis.

Results Nephropathic cystinosis is a rare disorder of cystine metabolism. Although renal failure is the earliest and most severe complication of this condition, all organs of the body eventually become involved. The brains of children with cystinosis demonstrate structural changes early in life. Neuro-cognitive differences, including motor incoordination and visual spatial dysfunction, are present from early life and may negatively impact learning. Executive functioning is also impaired and this may contribute to poor adherence to medication regimens.

Conclusions Early recognition of these difficulties allows for intervention to minimize problems associated with the neurocognitive deficits in cystinosis.

Keywords Nephropathic cystinosis, Visual spatial function, Motor coordination, Brain imaging

Nephropathic cystinosis is a rare lysosomal storage disorder of cystine accumulation. Although renal problems and failure to thrive are the earliest symptoms of the condition, multiple organs in the body are affected at some time in life. Awareness of possible central nervous system involvement was first described over 40 years ago. An early report by Ehrich et al. [18] described a patient with cystinosis who had cerebral atrophy and ventricular dilatation as well as seizures. Neuropathological studies showing the presence of cystine crystals in choroid plexus and meninges followed a few years later [14, 28, 29, 38, 54]. The findings of crystals in the choroid plexus suggested that children with cystinosis might develop hydrocephalus, and subsequent reports described hydrocephalus and brain atrophy in teens and young adults with cystinosis [14]. Soon after, direct brain involvement was described in additional case reports of neuropathological changes in cystinosis, with cystine crystals identified in brain tissue in high concentrations and in a widespread distribution in the brain, primarily in perivascular macrophages and oligodendrocytes [9, 54].

Early reports of clinical neurological manifestations of cystinosis were described in isolated case reports, and generally thought to be secondary to systemic complications such as renal failure and other metabolic imbalance [10, 14, 38]. Interest in the clinical manifestations caused by nervous system involvement in cystinosis was first noted in 1982, when Wolff et al. described the results of psychosocial and intellectual development in 12 children with cystinosis. Despite the fact that most of the children were in renal failure, they had general intelligence within the normal range, reportedly were performing satisfactorily in school (although no formal testing was performed) and were said to be "somewhat shy". The first study of detailed cognitive and neurological function in cystinosis [47] reported gross and fine motor incoordination and generalized hypotonia in a majority of individuals with cystinosis in that study, suggesting widespread, albeit nonspecific neurological involvement. The report

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also identified a specific cognitive deficit in visual spatial functioning in the 22 children and adults with cystinosis who participated in the study. Using standardized tests, global intellectual functioning was found to be normal, as were speech and language skills, compared to population norms. However, a specific cognitive profile emerged that showed a deficiency in visual spatial skills and visual spatial memory in approximately half of the children and adults with cystinosis compared to population means expected for age. These findings pointed to a more focally defined abnormality in brain function and led to further studies of brain structure and function in cystinosis (see below).

Imaging of the brain in the form of computed axial tomography (CT scan) and magnetic resonance imaging (MRI) has been used for many years to define structural differences in the brains of cystinosis patients. There have been frequent findings of cerebral atrophy [14, 18, 21, 1, 33] and Curie et al. [15] found a correlation between the degree of atrophy and cognitive function in children and young adults with cystinosis, whereas Servais et al. did not find an association between atrophy and cognition in a group of adults with cystinosis [41].

With the advent of life-sustaining treatment for the kidney disease in the form of successful renal transplantation and more recently treatment with cystine depleting agents [27], individuals with cystinosis are living longer and in better health than was possible prior to that time. At the same time, it has become increasingly evident that the nervous system is involved in cystinosis, and there are several possible neurological and cognitive complications that may occur. These include cognitive and motor dysfunction [1, 3, 21, 39, 47], feeding, swallowing and oromotor dysfunction [19, 43, 44, 48, 52], idiopathic intracranial hypertension [17, 37], myopathy [13, 26], seizures [18, 38], strokes and vasculopathy [6, 32, 51], Chiari I malformations [36], and encephalopathy [10–12, 30, 31]. The remainder of this review will focus on the neurocognitive complications of nephropathic cystinosis.

Since the initial reports of visual spatial and visual motor dysfunction in children with cystinosis, a number of publications have confirmed and extended our knowledge of cognitive consequences of cystinosis. Visual spatial function refers to the ability to process visual stimuli and their relationship to other objects in space, to visualize images or scenarios in one's mind, and to remember where objects are in space. Examples of visual spatial processing are being able to watch someone perform a series of dance movements and being able to do the movements; reading a map; and orienting to direction in space (e.g., north, south). Visual spatial memory requires an added component of being able to remember where something was located in space, such as finding one's car in a parking lot. Visual motor function, also referred to as eye-hand coordination, refers to a complex skill set that incorporates the processing of visual information with the ability to integrate that with motor functioning, such as when trying to draw a complex figure (e.g., a three-dimensional box or a clock, or when drawing a figure made up of other smaller figures [39].

Most individuals with cystinosis have difficulty with visual spatial processing and memory and with visual motor coordination [1, 3, 7, 40, 45]. This has been observed even in young children with cystinosis, and has suggested an early influence on brain development [49, 53]. These problems do not appear to be completely prevented by early treatment with cystine-depleting agents [53], suggesting that the cause may be a very early influence on brain development, and possibly a direct effect of the cystinosin gene mutation on brain development. Evidence for this possibility derives from two studies [34, 39] in which parents of children with nephropathic cystinosis, who are obligate heterozygotes for the gene mutation, were tested for visual spatial and visual motor functioning. In both studies, parents performed more poorly than unrelated adult controls on tests of visual spatial and visual motor functioning, suggesting that the observed cognitive dysfunction was not likely the result of cystine accumulation, since this would not explain the performance of otherwise unaffected carriers on these tasks.

Visual spatial functioning is thought to be subserved to a large extent by the parietal lobes of the brain [42]. A magnetic resonance imaging (MRI) study of brain white matter integrity using fractional anisotropy (FA) in children with cystinosis [5] demonstrated lower FA values in the white matter of both parietal lobes in the brains of children with cystinosis compared with measurements from the brains of children without cystinosis. FA is a measure of white matter integrity that allows for inferring degree of nerve fiber integrity, typically related to the integrity of myelination. Lower FA values than expected for age suggest deficiencies in white matter structural integrity, as might be seen with abnormal or delayed myelination. The results from the Bava study correlated with a measure of visual spatial performance, with lower performance scores associated with lower FA values, demonstrating a link between brain structure and cognitive changes in children with cystinosis. Specifically, lower FA values in the parietal lobes of children with cystinosis correlated directly with poorer visual spatial functioning, suggesting that structural integrity of the parietal white matter had been impaired in the cystinosis brain and may have been the cause of the observed cognitive changes.

Several other neuroimaging studies have been performed on children and adults with cystinosis in attempts

to identify potential markers of cognitive impairments. All have documented a high incidence of cerebral atrophy in children and adults with cystinosis, but with variable associations to cognitive performance [33, 1, 15, 41]. Visual motor/visual spatial function did not correlate with degree of cerebral atrophy in a study of 52 children with nephropathic cystinosis ages 2–17 years and 49 healthy control children [50]. Approximately one-third of the children in the study had mild to moderate cerebral atrophy on MRI scan. The presence of atrophy was not associated with the age of the child, nor was atrophy associated with the degree of motor coordination deficit in that cohort. Curie et al. [15] however, studied 17 children and adults with cystinosis as well as 16 healthy controls and found an inverse correlation between degree of cerebral atrophy on MRI scan and global intellectual functioning. The differences found in the 2 studies could be related to several factors. Techniques for measuring atrophy differed slightly between the studies, with one report using clinical interpretations by a pediatric neuroradiologist [50] and the second [15] using similar clinical neuroradiological readings but with more detail about quantification methods. Other factors that might account for differences in findings included age at which cystine-depleting agents was begun, degree of compliance with medications, inclusion of adults as well as children in the study, or other unknown genetic or environmental factors.

Another aspect of cognitive functioning that may be negatively impacted in cystinosis is executive functioning (EF). Executive functions are a set of cognitive skills that enable us to self-regulate, plan, focus attention, multitask, prioritize, set, and achieve goals. Successful executive functioning is of great importance in all aspects of life, including social, educational, and emotional well-being. Impairments in one or more areas of EF can make it more difficult to navigate daily decision-making, and in the face of adversity such as a chronic illness, can make it more difficult to succeed academically and socially, set goals, adhere to medication regimens, and plan for the future, among other challenges. Ballantyne et al. [4] studied EF in 28 individuals with cystinosis, age range 8–17 years, and 24 healthy controls in the same age range. None of the participants were in renal failure, and 8 had had successful renal transplants. Significant deficits in multiple areas and levels of EF were identified, including attention, initiation, motor speed, fluency, simultaneous processing, and speed of processing, as well as problems with higher-level skills including cognitive flexibility, managing increased processing demands, inhibiting prepotent responses, and abstract thinking, compared with typically developing controls. A related study using a parent report checklist [16] found a significantly higher risk of social problems in children with cystinosis compared to either a healthy control group or to another chronic disease control group (children with cystic fibrosis). A higher risk of attention problems was also identified in the cystinosis group compared with healthy controls. These findings may reflect early indicators of EF difficulties.

Brain electrical changes have rarely been used to investigate sensory processing in individuals with cystinosis using event-related brain potentials. One study of visual evoked brain electrical potentials demonstrated abnormal (delayed) early visual evoked potentials in 2 children with cystinosis in renal failure and on dialysis [20]. Following successful renal transplantation, visual evoked responses normalized, suggesting to the authors that the visual processing impairments might be reversible. However, no similar studies have been reported with children or adults with cystinosis who were in good general health and not in renal failure, and it is difficult to generalize conclusions from a 2-case study. A recent report [23] of auditory event-related brain potentials in a larger group of 25 children with cystinosis showed intact early auditory processing compared with neurotypical age-matched controls. However, their data suggested potential mild deficits in the maintenance of short-term auditory sensory memory, which in turn might lead to problems with working memory, or the ability to hold relevant information in short-term memory in order to use that information for a period of time. In a follow-up study, the same group used a similar electrophysiological paradigm to study 15 adults with cystinosis. They again documented intact early auditory sensory processing compared with a control group. There were also subtle differences between cystinosis and control groups that suggested the possibility that auditory sensory memory and certain aspects of attention might be impaired in cystinosis adults [22]. Future studies may help to more precisely define the presence and extent of a subtle auditory processing dysfunction in cystinosis.

Why are the findings of cognitive dysfunction in people with cystinosis important or relevant? Cognitive deficits, when found on testing, are rarely severe, and global intellectual function is almost always in the normal range (although somewhat lower than expected compared with unaffected controls— [7, 51, 55]. However, even mild impairments in visual spatial processing and memory can adversely affect early learning and academic achievement. School-age children with visual spatial deficits may have difficulty with learning to read and do math [2]. Handwriting may also be problematic due to visual motor problems. Even keyboarding may present challenges because of spatial dysfunction and motor incoordination. If there is an additional problem with executive

functioning, children may experience attention-deficit-like symptoms, as well as challenges with developing age-appropriate social skills. During adolescence, academic issues may plateau, but new challenges become evident as teens are taking on more independence from their parents. This may include medication management, doctor's appointments, and decisions about their health and well-being, as well as planning for the future beyond high school. It is at this time that deficits in executive functioning can become more obvious and impairing to the individual.

Fortunately, early identification of these potential problems will allow for intervention that can significantly improve overall levels of cognitive functioning and reduce some of the long-term problems mentioned above. Awareness of the potential for cognitive difficulties is important for parents and physicians caring for children with cystinosis. In early primary school years, parents and teachers should attend closely to the academic progress of their child. Is the child making good progress in comparison to classmates and to what would be expected for age and grade-level? Are there any warning signs, such as being slow at learning to recognize letters and numbers, learning to read or do basic arithmetic? Is the child experiencing challenges with printing letters or writing legibly? Is schoolwork organized and neatly presented as expected for age and grade level? Is the child showing signs of inattentiveness? If any warning signs are present, the next step would be to evaluate the child, possibly with a school psychologist or educational assessor, looking in particular for indicators of visual processing, visual spatial and motor coordination deficits. It is important to note that this type of assessment may not be typically conducted by school psychologists, and it may be necessary to request specific types of assessments in order to identify problem areas. Once identified, early intervention can be initiated in school utilizing several potential teaching formats. Children with cystinosis learn less easily with visual vs. verbal learning [46]. If given additional time, however, visual learning can improve. Thus, specific interventions (for example, emphasizing extended time to process visually presented information, auditory over visual learning, and multi-modality teaching) may result in sufficient gains that the child can continue to function at grade level. Occupational therapy may be very useful in improving visual motor and motor coordination skills. Sometimes more intensive intervention with small group or one on one teaching may be necessary for a variable period of time.

For older children and adolescents with executive dysfunction, the results can be very detrimental to health and well-being in terms of skipping medications and not following through on medical appointments and treatment recommendations. In these instances, merely telling the person what they should do and why they should do it is not enough to ensure adequate adherence. Rather, a regimen of involving the patient in active problem-solving and specific behavioral interventions can aid in improving responsiveness to medical advice and thus in better disease management. Many strategies have been proposed to aid individuals with similar EF challenges [8, 25, 35], Examples of behavioral interventions include providing structure and emphasizing the use of routines, breaking complex tasks into smaller steps, teaching organizational skills such as the use of planners and checklists, and using behavioral reinforcers to modify behaviors [35]. The use of cell phones, tablets, and other devices with alarms, reminders, and messaging capabilities can be utilized to reinforce memory and routines and aid in maintaining structure.

Despite the presence of specific cognitive deficits, the long-term outlook for cognitive and behavioral functioning can be positive, particularly if early recognition and intervention are instituted. Treatment with cystine-depleting agents very early in life may also lessen the severity of cognitive issues [15, 53]. In fact, a more recent study [24] of adults with cystinosis who had received long-term treatment with cystine-depleting agents showed no difference in performance on visual and verbal learning tasks compared with controls (although performance on the visual learning task was still somewhat lower than on the verbal learning task). This result should not be interpreted as indicating that no cognitive deficit remains, but that certain aspects of the cognitive challenges, specifically learning tasks, may be minimized with optimal medical care and early intervention.

Acknowledgments
Not applicable.

Authors' contributions
Dr. Trauner conducted a literature search and wrote the manuscript in its entirety. The author read and approved the final manuscript.

Funding
The author did not receive support from any organization for the submitted work.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
The two examples from research conducted in Dr. Trauner's laboratory consist of data obtained from an earlier study that was approved by the University of California San Diego Institutional Review Board. Informed consent was obtained from parents and participants prior to conducting the research studies.

Consent for publication
Not applicable.

Competing interests
Dr. Trauner is a member of the Medical Advisory Committee for the Cystinosis Research Network and a member of the Medical and Scientific Advisory Committee for the Cystinosis Research Foundation. She has also served in a limited advisory capacity to AvroBio and Horizon Therapeutics.
Dr. Trauner has received research funding in the past from the National Institutes of Health, the Cystinosis Research Network, the Cystinosis Research Foundation, and the Cystinosis Foundation.

Received: 7 February 2023 Accepted: 21 May 2023
Published online: 01 July 2023

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